Prophylactic antibiotic use following cardiac arrest: a systematic review and meta-analysis

Keith Couper PhD[1,2], Ryan Laloo[1], Richard Field[1], Gavin D Perkins MD[1,2], Matthew Thomas[3], Joyce Yeung PhD[1,2]

1) Critical Care Unit, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

2) Warwick Medical School, University of Warwick, Coventry, UK

3) Critical Care Unit, University Hospitals Bristol NHS Foundation Trust, Bristol, UK

Corresponding author: Dr Joyce Yeung, Clinical Trials Unit, Warwick Medical School, University of Warwick, Coventry, UK. Email: j.yeung.4@warwick.ac.uk. Tel: +44 (0) 2476 574 880

Conflicts of interest and sources of funding:

The authors declare no conflicts of interest.

KC and JY are supported by NIHR post-doctoral research fellowships. GDP is supported as a NIHR Senior Investigator. Financial support: No external funding

Terms for indexing:

Review; Heart arrest; Anti-Bacterial Agents; Pneumonia; Mortality; Critical care

Word count

Abstract 271 words

Main manuscript 3028 words

Abstract

Objective: To evaluate the effect of prophylactic/ early antibiotics (intervention group) compared with clinically driven/ delayed antibiotics (control group) on patient and infectious outcomes in adult cardiac arrest patients admitted to hospital

Data Sources: We searched MEDLINE (1946-current), EMBASE (1947-current) and the Cochrane library (inception-current) on 8th May 2018. Additional citations were identified through forward and backward citation tracking.

Study Selection: Two reviewers independently screened titles, abstracts, and full-texts. We included observational and interventional primary research studies with a concurrent or retrospective control group that were relevant to our study objective.

Data Extraction: We extracted data using a piloted data extraction form. Risk of bias was assessed using the Cochrane tool for randomised controlled trials or the GRADE tool for risk of bias in observational studies. Overall evidence quality for each outcome was assessed using the GRADE system.

Data Synthesis: Databases searches and citation tracking identified 6825 citations, of which ten citations containing 11 studies (3 randomised controlled trials, 8 observational studies) were eligible for inclusion. Data were summarised in meta-analyses using random-effect models. The intervention was not associated with increased survival (odds ratio 1.16, 95% CI 0.97 to 1.40), survival with good neurological outcome (odds ratio 2.25, 95% CI 0.93 to 5.45), critical care length of stay (mean difference -0.6, 95% CI -3.6 to 2.4) or incidence of pneumonia (odds ratio 0.58, 95% CI 0.23 to 1.46). Findings were generally consistent between observational studies and randomised controlled trials.

Conclusions: Antibiotic prophylaxis following cardiac arrest is not associated with a change in key clinical outcomes. Further high-quality trials may be needed to address this important clinical question.

Review registration: PROSPERO CRD42016039358.

In patients that are successfully resuscitated following cardiac arrest, many suffer clinical complications on the intensive care unit.(1) Pneumonia is a common infective complication that affects between approximately 50% and 60% of patients.(1-4) This is likely caused by aspiration during the cardiac arrest event or development of ventilator associated pneumonia. The development of pneumonia on the intensive care unit following cardiac arrest is associated with increased length of critical care stay.(4, 5)

A key clinical challenge following cardiac arrest is the accurate identification of infective complications.(6) In particular, inflammatory processes and neurological dysfunction that form part of the post-cardiac arrest syndrome, together with the use of targeted temperature management, make traditional indicators of infection such as pyrexia and leucocytosis challenging to use in this population.(7)

On this basis, a strategy of early prophylactic antibiotics may seem reasonable in the post-arrest population. However, this strategy must be balanced against the global public health concerns of antimicrobial resistance.(8) Current resuscitation guidelines do not provide guidance on antibiotic usage.(9) The aim of this systematic review is to evaluate the effect of early antibiotic use on key clinical outcomes in adult patients resuscitated from cardiac arrest.

Methods

We conducted this systematic review in accordance with a protocol that was registered with PROSPERO on 1st June 2016 (CRD42016039358). This report is written in accordance with the PRISMA guideline.(10)

Search strategy

We searched MEDLINE (1946-current), EMBASE (1947-current) and the Cochrane library (inception-current) on 8th May 2018. Searches included a combination of MESH heading and keywords. An example search strategy is included in the electronic supplement. Following search completion and deletion of duplicate citations, two authors (KC/RL) independently screened titles, abstracts, and article full-texts. Disagreements were resolved through discussion or, where needed, review by a third author (JY). Additional potentially relevant citations were identified through forward and backward citation tracking of included papers.

Study inclusion criteria and outcomes

Observational and interventional primary research studies were eligible for review inclusion if they compared the effect of administration of early/ prophylactic antibiotics with delayed/ clinically-driven administration of antibiotics in adult patients following cardiac arrest. We included all study types that included a control group. Case reports and case series were not eligible for inclusion. There was no restriction on language or publication date.

The co-primary study outcomes were survival and survival with good neurological outcome. Secondary outcomes included critical care length of stay, infective complications (for example, pneumonia), duration of mechanical ventilation, duration of antibiotic administration, and incidence of positive bacterial cultures.

Risk of bias

The risk of bias in individual studies was assessed independently by two authors (KC/RL), with disagreements resolved through discussion or arbitration by a third reviewer (JY). Risk of bias in

randomised controlled trials was assessed using the Cochrane risk of bias assessment tools.(11) Risk of bias in observational studies was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool.(12) We assessed risk of publication bias through visualisation of funnel plots where sufficient studies were available. For each outcome, we used the GRADE system to categorise the overall quality of evidence.(13)

Data extraction

A data extraction form was developed and pilot-tested. Data were extracted to the extraction form by one author (KC), and checked for accuracy by a second author (RL). Where available and appropriate, additional relevant information was extracted from the study clinical trial registration. We did not contact study authors for further data.

Data synthesis

We used meta-analyses to synthesise evidence by outcome, where this approach was not precluded. A random-effects model was used to compute the odds ratio (OR) and 95% confidence interval for dichotomous outcomes, and mean difference and 95% confidence interval for continuous outcomes. We measured statistical heterogeneity using the Higgins I^2 statistic.(14) For observational studies where more than one type of analysis was reported, we preferentially used adjusted or matched case analyses, over unadjusted analyses in meta-analyses. We used Review Manager (RevMan) (Version 5.3, Copenhagen, Denmark) to perform meta-analyses. We planned sub-group analyses to examine potential sources of heterogeneity. In particular, we planned to examine the effect of study design (observational compared with interventional) and clinical factors (in-hospital cardiac arrest compared with out-of-hospital cardiac arrest; mild therapeutic hypothermia v no therapeutic

hypothermia; and type of infective complication). In addition, we undertook two sensitivity analyses that were not defined a priori to test the robustness of our findings. Firstly, we assessed the impact of our hierarchical approach to selection of analysis type in observational studies by testing the use of other analyses on overall findings. Secondly, where observational studies reported additional analyses to assess the impact of immortal time bias on study findings, we tested the effect of using these data on overall findings.(15, 16)

Results

Database searches identified 6794 citations, with a further 31 citations identified through citation tracking (figure one). After duplicate removal and exclusion of studies based on title/ abstract, we assessed the eligibility of 63 full-text papers. From these, we included 11 studies from ten citations.(5, 17-25)

The eleven eligible studies comprised three randomised controlled trials and eight observational studies (table one). Studies were conducted in Europe (n=8), Asia (n=2), and across Europe and North America (n=1). One study included only patients treated prior to the publication of the seminal papers on post-arrest mild therapeutic hypothermia in 2002, although the study did include some patients that were recruited to the one of these trials. Across the eleven studies, there were a total of 6149 patients (median per study 138, interquartile range 64-733). All studies included OHCA patients, of which one also included IHCA patients.

Within studies, there were two distinct comparisons. The three randomised controlled trials and three observational studies compared the use of prophylactic antibiotics with a clinically-driven approach to antibiotic administration. In contrast, the remaining observational studies compared the

administration of antibiotics within a specific timeframe with non-administration of antibiotics in that timeframe.

Risk of bias and evidence quality

A summary of the risk of bias assessments and funnel plots are included in the electronic supplement. Two of the randomised controlled trials are reported only as abstracts, such that most elements were considered to be of unclear risk of bias. All observational studies were considered to be at high risk of bias, due to confounding, even where adjusted analyses were used. Observational studies were also prone to the risk of immortal time bias as patients may have died early in their critical care admission prior to receiving antibiotics, thereby tending to favour the intervention group.(15, 16)

For evidence quality, as assessed by the GRADE system, our starting point for evidence quality was determined by whether observational studies or randomised controlled trials made the largest contribution to the number of patients for that outcome. We downgraded most outcomes for indirectness due to the subtle differences in clinical question asked by different studies. No publication bias was detected for any outcome. GRADE tables are included in the electronic supplement.

Outcomes

The outcome of survival at last recorded time point was reported in eight studies (three RCTs, one observational study with adjusted analysis, three observational studies with unadjusted analysis) comprising 3443 patients.(17-19, 21, 23-25) Studies analysed survival at different time points, namely ITU discharge (three studies), hospital discharge (one study), 28-day (one study), 30-day (two studies), and six-month (one study). Of these, seven studies were included in a meta-analysis (figure

2a). The overall treatment effect showed no benefit to the intervention (odds ratio of survival at last recorded time point 1.16, 95% CI 0.97 to 1.40). Overall, statistical heterogeneity was low (I^2=0%). Heterogeneity between randomised trial and observational study sub-groups was moderate-substantial (I^2=55.9%), and the direction of effect differed between sub-groups. The study not included in the meta-analysis, due to the method in which results were reported, generated similar findings to those of the meta-analysis.(21) Evidence quality was assessed as very low.

Survival with good neurological outcome at last recorded time point was reported in five studies (one RCT, one observational study with adjusted analysis, three observational studies with unadjusted analysis) comprising 2246 patients.(18, 20, 22, 24) Measurement time point differed between studies, namely ICU (three studies), hospital (one study), and six-month (one study). Meta-analysis of these five studies showed no benefit to intervention treatment (OR 2.25, 95% CI 0.93 to 5.45), although heterogeneity was considerable (I^2=83%) and the confidence interval was wide (figure 2b). Kocjancic et al presented data broken down by initial rhythm, such that it is reported over two lines in the forest plot.(20) This study also drove much of the statistical heterogeneity identified, and it was also noted to be clinically heterogeneous in that the study intervention comprised the implementation of an intensive post-resuscitation care bundle, where the independent effect of antibiotic use was evaluated in a regression model.(20) Exclusion of this study from the meta-analysis markedly reduced the reported statistical heterogeneity (I^2=0%) and led to a decrease in the point estimate, but did not affect the direction of effect or overall finding (OR 1.21, 95% CI 0.94 to 1.56). Evidence quality was assessed as very low.

Critical care length of stay was reported in five studies (two RCTs, three observational with unadjusted analyses) comprising 1448 patients.(18, 22, 24, 25) Three studies were included in a meta-analysis (see electronic supplement) which found no benefit to intervention (mean difference -0.6, 95% CI -3.6 to 2.4). The substantial heterogeneity (I^2=61%) was driven by differences between

the two randomised controlled trials, rather than differences between study design. Kim et al and Gagnon et al reported only median and interquartile range, so could not be included in the meta-analysis.(22, 24) However, in line with the results of the meta-analysis, these studies reported no difference between the control and intervention group. Evidence quality was assessed as very low.

Duration of invasive mechanical ventilation was reported in two randomised controlled trials, which recruited a total of 87 patients.(18, 25) The intervention (see electronic supplement) was not associated with a reduction in mechanical ventilation duration (mean difference -2.5, 95% CI -8.8 to 3.9), although heterogeneity was substantial (I^2=77%), studies were small and likely to be underpowered. Evidence quality was assessed as low.

Duration of antibiotic administration was not reported in any study.

Pneumonia diagnosis was reported in six studies (2 RCTs, 3 observational studies with adjusted analyses, 1 observational studies with unadjusted analyses) recruiting 5008 patients.(5, 17, 18, 23, 24, 26) All studies, where it was defined, required chest x-ray changes for a pneumonia diagnosis, but additional criteria varied ranging from none to the need for a mix of a hypoxaemia, positive respiratory microbiology, and tracheal secretions. Only one study incorporated leucocytosis and pyrexia in its pneumonia diagnosis. The time point for pneumonia diagnosis was not typically defined.

In our meta-analysis (figure 3), the intervention was not associated with a reduced likelihood of pneumonia (OR 0.58, 95% CI 0.23 to 1.46). Heterogeneity was considerable, but was primarily driven by Gagnon et al's study. Exclusion of this study reduced heterogeneity (I^2=48%) and decreased the magnitude of the effect, but did not affect the direction of effect or overall finding (OR 0.87, 95% CI 0.62 to 1.23). The study by Gagnon et al also reported the effect of the intervention on other infective complications (any serious infection, sepsis) - in line with the study's pneumonia analysis, prophylactic antibiotics were reported to significantly reduce the incidence of these events, although the study was at high risk of confounding bias.(26) Evidence quality was assessed as very low.

The outcome of positive microbiology was reported in three studies (two randomised controlled trials, one observational study) which recruited 155 patients.(18, 24, 27) Due to variability in outcome definitions in relation to sample source and time point, these data were not meta-analysed. Two studies reported a reduced incidence of positive respiratory microbiology in the first three days in patients treated with prophylactic antibiotics (18, 27), but this effect did not appear to continue after day four or extend to other sites, such as blood. Evidence quality was assessed as low.

Sub-group and sensitivity analyses

We were unable to perform the pre-defined sub-group analyses of clinical factors due to the absence of relevant studies.

Our first group of sensitivity analyses in which adjusted analyses were replaced with unadjusted analyses were performed for the outcomes of survival (1 study) and pneumonia (2 studies). These replacements made no difference to our overall findings (data not shown). Our second group of sensitivity analyses explored the robustness of findings when we used analyses that accounted for immortal time bias. We performed these sensitivity analyses for three outcomes: mortality (1 study), critical care length of stay (1 study), and duration of mechanical ventilation (1 study). These analyses were similar to our main analyses (data not shown).

Discussion

This systematic review and meta-analysis of 11 studies, which included data on 6149 patients, examined the effect of antibiotic administration following cardiac arrest on key clinical outcomes.

We found that early/ prophylactic antibiotic administration had no effect on clinically-important outcomes, such as survival, intensive care length of stay, and incidence of pneumonia. However, it may be associated with a reduction in positive respiratory microbiology in the first few days after the cardiac arrest.

Several factors may explain these findings. Firstly, in relation to survival outcomes, cause of death in patients that die on the intensive care unit following out-of-hospital cardiac arrest is typically attributed to cardiac or neurological failure.(1, 28) In these patients, antibiotics seem unlikely to modify the mechanism of death. In the targeted temperature management trial (TTM) trial, 82% of deaths were attributed to these causes.(1) In contrast, death from multi-organ failure secondary to septic shock, where antibiotic prophylaxis may be clinically beneficial, was identified as the cause of death in only 12% of cases.(1)

Secondly, epidemiological studies report the wide variety of gram-positive and gram-negative bacteria isolated from the respiratory tract following cardiac arrest. Commonly reported bacteria include staphylococcus aureus, streptococcus pneumonia, escherichia coli, haemophilus influenza/ parainfluenzae, and klebsiella pneumoniae.(2) The choice of antibiotic will likely be driven by local ecology, but nevertheless some patients may be infected by bacteria that are not sensitive to the chosen antibiotic selected for prophylactic treatment. For example, co-amoxiclav, which was the antibiotic used in the three randomised controlled trials, will not reliably treat the wide range of bacteria that may be present following cardiac arrest.(29)

Finally, the acidity of gastric contents means that bacteria may not be present, such that distinguishing aspiration pneumonia from aspiration pneumonitis is clinically challenging.(30) In the post-arrest patient, the patient's pro-inflammatory state together with targeted temperature management treatment increases the challenge of reliably identifying infection, such that clinicians may have a low threshold for commencing antibiotics in the days following a cardiac arrest.(6, 7) In one randomised controlled trial, over 50% of patients in the control arm (clinically-driven antibiotics)

received antibiotics by the third day following admission.(18) Whilst this may reflect the reality of clinical practice, it may mean that in the context of a trial, there is insufficient separation of treatment arms to detect a clinically important and statistically significant effect.

Our finding that prophylactic antibiotics were not associated with a decrease in pneumonia contrasts with previous critical care studies that have recruited a general population comatose patients.(31-33) Whilst these studies consistently reported a reduction in pneumonia, no effect on mortality or length of stay was observed. The reason for this difference is unclear, but may reflect differences in patient population in terms of the risk of developing infective complications.

The targeted temperature management trial found that maintaining a temperature of 33°c following cardiac arrest was not superior to a temperature of 36°c.(1) These trial results have led to a shift in clinical practice, such that clinicians now tend to manage patients at 36°c following cardiac arrest.(34-36) Whilst the TTM trial found no difference in pneumonia incidence between study arms, several observational studies have reported a decreased incidence of pneumonia in patients treated at 36°c.(5, 37) This change in practice may therefore reduce the need for antibiotic use following cardiac arrest.

Our review findings should be seen in the context of risks associated with a treatment strategy of antibiotic prophylaxis including cost and adverse effects, such as allergy/ anaphylaxis, gastrointestinal effects, clostridium difficile infection, and development of antibiotic resistance.(38, 39) At a societal level, antimicrobial resistance has been recognised as a global health concern, leading to an international drive to rationalise antimicrobial usage.(8)

Two recent review papers have developed protocols to describe best practice in antibiotic administration following cardiac arrest.(6, 40) Whilst seemingly not based on a systematic review of the evidence, both reviews recommend that only patients with positive respiratory microbiology or objective evidence of aspiration (e.g. gastric contents on bronchoscopy) should be commenced on antibiotics. In the trial by Ribaric et al, such patients were excluded from the trial and represented

22% of patients screened.(18) On this basis, these recommendations seem consistent with the findings of this systematic review.

This review has several limitations. Firstly, evidence quality for all outcomes was assessed as being low or very low, highlighting the need for further high-quality evidence in this area. Secondly, analysis was made challenging by heterogeneity across studies in relation to methodology, the specific nature of the intervention, and measurement of outcomes. The recent publication of a core outcome set for cardiac arrest trials is welcomed as a way to reduce outcome heterogeneity in future studies.(41) Thirdly, all but one of the index studies recruited only out-of-hospital cardiac arrest patients. Due to differences in aetiology, our review results may not be generalizable to the in-hospital cardiac arrest population. Fourthly, we pre-defined several sub-group analyses based on clinical factors. Other factors, such as cardiac arrest duration, may also alter the risk of infection following cardiac arrest. Limitations in the available evidence precluded analysis of these factors. As such, it remains unknown whether prophylactic antibiotics affect outcome in key sub-groups. Finally, changing practice in relation to temperature management following cardiac arrest may limit the generalisability of some review data to current clinical practice.

Conclusion

In this review, antibiotic prophylaxis was not associated with an improvement in any important clinical outcome, when used following cardiac arrest. As such, current data does not support the use of prophylactic antibiotics in patients following cardiac arrest. Further high-quality trials may be needed to address this important clinical question.

1. Nielsen N, Wetterslev J, Cronberg T, et al. Targeted Temperature Management at 33°C versus 36°C after Cardiac Arrest. New England Journal of Medicine 2013;369(23):2197-2206.

2. Mongardon N, Perbet S, Lemiale V, et al. Infectious complications in out-of-hospital cardiac arrest patients in the therapeutic hypothermia era*. Critical Care Medicine 2011;39(6):1359-1364.

3. Tsai M-S, Chiang W-C, Lee C-C, et al. Infections in the survivors of out-of-hospital cardiac arrest in the first 7 days. Intensive Care Med 2005;31(5):621-626.

4. Hellenkamp K, Onimischewski S, Kruppa J, et al. Early pneumonia and timing of antibiotic therapy in patients after nontraumatic out-of-hospital cardiac arrest. Critical Care (London, England) 2016;20:31.

5. Perbet S, Mongardon N, Dumas F, et al. Early-onset pneumonia after cardiac arrest: characteristics, risk factors and influence on prognosis. Am J Respir Crit Care Med 2011;184(9):1048-1054.

6. Johnson NJ, Carlbom DJ, Gaieski DF. Ventilator Management and Respiratory Care After Cardiac Arrest: Oxygenation, Ventilation, Infection, and Injury. Chest 2018;153(6):1466-1477.

7. Nolan JP, Neumar RW, Adrie C, et al. Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. A Scientific Statement from the International Liaison Committee on Resuscitation; the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; the Council on Stroke. Resuscitation 2008;79(3):350-379.

8. World Health Organisation. Global action plan on antimicrobial resistance. 2015 [cited 24/07/2018]Available from: http://apps.who.int/iris/bitstream/handle/10665/193736/9789241509763_eng.pdf?sequence=1

9. Nolan JP, Soar J, Cariou A. European Resuscitation Council and European Society of Intensive Care Medicine guidelines for post-resuscitation care 2015: Section 5 of the European Resuscitation Council Guidelines for Resuscitation. Resuscitation 2015;95.

10. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009;151(4):264-269.

11. Higgins J, Green S, (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. 2011 [cited 2/3/2014]Available from: www.cochrane-handbook.org

12. Guyatt GH, Oxman AD, Vist G, et al. GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). Journal of clinical epidemiology 2011;64(4):407-415.

13. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. Journal of clinical epidemiology 2011;64(4):383-394.

14. Higgins JPT, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327(7414):557-560.

15. Andersen LW, Grossestreuer AV, Donnino MW. "Resuscitation time bias"—A unique challenge for observational cardiac arrest research. Resuscitation 2018;125:79-82.

16. Lévesque LE, Hanley JA, Kezouh A, et al. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. BMJ 2010;340.

17. Daix T, Cariou A, Meziani F, et al. Short term antibiotics prevent early VAP in patients treated with mild therapeutic hypothermia after cardiac arrest. Critical Care Conference: 38th International Symposium on Intensive Care and Emergency Medicine, ISICEM 2018;22.

18. Ribaric SF, Turel M, Knafelj R, et al. Prophylactic versus clinically-driven antibiotics in comatose survivors of out-of-hospital cardiac arrest-A randomized pilot study. Resuscitation 2017;111:103-109.

19. Davies KJ, Walters JH, Kerslake IM, et al. Early antibiotics improve survival following out-of hospital cardiac arrest. Resuscitation 2013;84(5):616-619.

20. Kocjancic ST, Jazbec A, Noc M. Impact of intensified postresuscitation treatment on outcome of comatose survivors of out-of-hospital cardiac arrest according to initial rhythm. Resuscitation;85(10):1364-1369.

21. Skrifvars MB, Pettila V, Rosenberg PH, et al. A multiple logistic regression analysis of in-hospital factors related to survival at six months in patients resuscitated from out-of-hospital ventricular fibrillation. Resuscitation;59(3):319-328.

22. Gagnon DJ, Nielsen N, Fraser GL, et al. Prophylactic antibiotics are associated with a lower incidence of pneumonia in cardiac arrest survivors treated with targeted temperature management. Resuscitation 2015;92:154-159.

23. Tagami T, Matsui H, Moroe Y, et al. Early antibiotics administration during targeted temperature management after out-of-hospital cardiac arrest: A nationwide database study. BMC Anesthesiology;16(89).

24. Kim SJ, Lee JK, Kim DK, et al. Effect of Antibiotic Prophylaxis on Early-Onset Pneumonia in Cardiac Arrest Patients Treated with Therapeutic Hypothermia. Korean J Crit Care Med 2016;31(1):17-24.

25. Bongaerts D, Hendriks B, Gordts B, et al. Antibiotic prophylaxis is superior to selective antibiotic therapy in patients treated with therapeutic hypothermia after out-of-hospital cardiac arrest. Intensive Care Med 2013;39(SUPPL. 2):S287.

26. Gagnon DJ, Nielsen N, Fraser GL, et al. Prophylactic antibiotics are associated with a lower incidence of pneumonia in cardiac arrest survivors treated with targeted temperature management. Resuscitation;92:154-159.

27. Bongaerts D, Hendriks B, Gordts B, et al. Antibiotic prophylaxis is superior to selective antibiotic therapy in patients treated with therapeutic hypothermia after out-of-hospital cardiac arrest. Intensive Care Med;2:S287.

28. Laver S, Farrow C, Turner D, et al. Mode of death after admission to an intensive care unit following cardiac arrest. Intensive Care Med 2004;30(11):2126-2128.

29. American Thoracic Society and the Infectious Diseases Society of America. Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia. American Journal of Respiratory and Critical Care Medicine 2005;171(4):388-416.

30. Marik PE. Aspiration Pneumonitis and Aspiration Pneumonia. New England Journal of Medicine 2001;344(9):665-671.

31. Sirvent JM, Torres A, El-Ebiary M, et al. Protective effect of intravenously administered cefuroxime against nosocomial pneumonia in patients with structural coma. American Journal of Respiratory and Critical Care Medicine 1997;155(5):1729-1734.

32. Acquarolo A, Urli T, Perone G, et al. Antibiotic prophylaxis of early onset pneumonia in critically ill comatose patients. A randomized study. Intensive Care Med 2005;31(4):510-516.

33. Vallés J, Peredo R, Burgueño MJ, et al. Efficacy of Single-Dose Antibiotic Against Early-Onset Pneumonia in Comatose Patients Who Are Ventilated. CHEST 2013;143(5):1219-1225.

34. Nolan JP, Ferrando P, Soar J, et al. Increasing survival after admission to UK critical care units following cardiopulmonary resuscitation. Critical Care 2016;20(1):1-10.

35. Deye N, Vincent F, Michel P, et al. Changes in cardiac arrest patients' temperature management after the 2013 "TTM" trial: results from an international survey. Annals of Intensive Care 2016;6(1):4.

36. Salter R, Bailey M, Bellomo R, et al. Changes in Temperature Management of Cardiac Arrest Patients Following Publication of the Target Temperature Management Trial. Critical Care Medicine 9000;Online First.

37. Bray JE, Stub D, Bloom JE, et al. Changing target temperature from 33°C to 36°C in the ICU management of out-of-hospital cardiac arrest: A before and after study. Resuscitation 2017;113:39-43.

38. Tamma PD, Avdic E, Li DX, et al. Association of adverse events with antibiotic use in hospitalized patients. JAMA Internal Medicine 2017;177(9):1308-1315.

39. Costelloe C, Metcalfe C, Lovering A, et al. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. BMJ 2010;340.

40. Kakavas S, Mongardon N, Cariou A, et al. Early-onset pneumonia after out-of-hospital cardiac arrest. Journal of Infection 2015;70(6):553-562.

41. Haywood K, Whitehead L, Nadkarni VM, et al. COSCA (Core Outcome Set for Cardiac Arrest) in Adults: An Advisory Statement From the International Liaison Committee on Resuscitation. Resuscitation 2018;127:147-163.